

New anticoagulant drugs : monitoring and perioperative strategies

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Abstract : Arterial and venous thromboses are major causes of mortality and morbidity. In Western countries, more than 1% of the population takes an antithrombotic agent. Many of these patients will need to undergo surgery and decisions need to be made regarding whether to continue their antithrombotic medication and risk increased bleeding or to stop it and potentially increase the risk of thrombosis. Anaesthesiologists, therefore, need to be aware of the basic pharmacology of the available agents as well as their individual indications, contraindications, and adverse effects. In this review we will discuss these aspects, and also discuss new antithrombotic agents that are currently being developed to improve efficacy and to increase safety in comparison with conventional agents. New coagulation monitoring devices will also be discussed.

INTRODUCTION

Antithrombotic agents include antiplatelet agents and anticoagulants⁴¹. There is still some concern over which strategy should be applied to antithrombotic agents during invasive procedures (33). The perioperative management of patients with coronary stents, bare metal or drug eluting stents, who are taking antithrombotic agents, is a particularly hot topic of debate (2, 3, 4, 36). Currently available parenteral anticoagulants include heparin, low molecular weight heparin (LMWH), and fondaparinux (5). LMWH is gradually replacing heparin for the treatment of most patients with venous thromboembolism and acute coronary syndrome (ACS) because LMWH has similar efficacy but is more convenient and cost-effective than heparin. Moreover LMWH has superior bioavailability, a long half-life, a more predictable anticoagulant effect, and fewer bleeding complications. In addition, monitoring is not required which is a major advantage for outpatient treatment. For long-term use, coumarin derivatives are the only oral anticoagulant currently available ; these have a narrow therapeutic window because their metabolism is under genetic control and is greatly influenced by dietary factors and concomitant medication. Consequently, time consuming and expensive monitoring is essential to ensure that a

therapeutic effect is achieved. Because of these limitations, the search for more effective and safer antithrombotics continues and new drugs are regularly introduced into clinical practice (41). However, the expectation set in some anticoagulant drugs was not obtained and perioperative strategies for antiplatelet agents have to be adapted since the last 5 years (20).

THROMBOGENESIS

The initiation of coagulation in arteries and veins is triggered by the binding of activated FVII, which circulates in small amounts in the blood, with tissue factor (TF), a nonvascular cellular receptor expressed on nonvascular cells as a result of tissue injury or by monocytes as a result of inflammation. Once formed, the TF-FVIIa complex activates factor X and factor IX. FXa converts small amounts of prothrombin into thrombin. This small amount is sufficient to activate platelets, factor V, factor VIII, and factor XI. These thrombin-mediated factors are essential for the propagation of coagulation. On the surface of the activated platelets, FIXa binds to FVIIIa to form intrinsic tenase, which activates FX. Subsequently, FXa binds to FVa on the activated platelets to form the prothrombinase complex. These processes are both calcium-dependent. The prothrombinase complex then produces the thrombin burst. Only this large amount of thrombin is able to convert fibrinogen to fibrin. In addition, thrombin activates the protein C-protein S pathway which limits the coagulation activation to the site of injury (32). Platelets are essential for coagulation to take place and act as a scaffold to keep the different elements in place. Thrombin is also crucial and control of its generation or action will reduce the clotting process.

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Pathologic thrombosis occurs when procoagulant stimuli overwhelm the natural anticoagulant and fibrinolytic systems (26). Arterial thrombosis is usually initiated by spontaneous rupture of atherosclerotic plaques. These thrombi, formed under high shear stress, are composed primarily of platelet aggregates held together with fibrin strands. Obstruction of arterial flow leads to ischaemia, which manifests as unstable angina or myocardial infarction, and stroke or limb ischaemia if cerebral or peripheral vessels are involved. Venous thrombi, which form under low flow conditions, are predominantly composed of fibrin and red cells. Thrombi may develop anywhere in the venous system but most commonly arise in the deep veins of the legs through an interplay among venous stasis, hypercoagulability, and vessel damage. Venous thrombosis might lead to postphlebotic syndrome or pulmonary embolism; the latter with potentially fatal consequences (41).

ANTITHROMBOTIC AGENTS

Current antithrombotic agents consist of antiplatelet agents and anticoagulants. Antiplatelet drugs are the reference antithrombotic agents for the prevention and treatment of arterial thrombosis. Antiplatelet agents are often combined with anticoagulants at least in the acute phase of arterial thrombosis. Anticoagulants are the drugs of choice in the prevention and treatment of venous thromboembolic disease. Anticoagulants are also still the main choice in patients with mechanical heart valves (41), and/or a history of atrial fibrillation (35).

Platelet aggregation inhibitors

Since the platelets are the mainstay of new clot formation and progression of coagulation, qualitative and quantitative inhibition of platelet activation have been widely used in patients with acute coronary syndrome, myocardial infarction, stroke, peripheral arterial thrombosis, and in patients undergoing endovascular coronary intervention and stent implantation.

Currently, there are three major classes of antiplatelet drugs in use. The first and oldest class is acetylsalicylic acid; the second class comprises the thienopyridines, ticlopidine and clopidogrel. These drugs irreversibly inhibit thromboxane and ADP-mediated aggregation, respectively, but their antiplatelet effect is only partial. The third class of antiplatelet drugs includes inhibitors of the platelet

receptor, glycoprotein GPIIb/IIIa. The platelet glycoprotein receptor represents the common pathway in platelet aggregation and drugs interfering with this pathway are among the most powerful inhibitors of platelet function. This category of antiplatelet agents includes monoclonal antibodies against the receptor (abciximab) and compounds that compete with fibrinogen and von Willebrand factor for receptor binding (eptifibatide, tirofiban).

The benefits of aspirin have been widely documented and aspirin remains the cornerstone for the prevention and treatment of arterial thrombosis (33). Clopidogrel is approved for the reduction of ischaemic events in patients with myocardial infarction (MI), stroke, and peripheral arterial disease. Dual therapy of aspirin with clopidogrel is recommended for a period of 4 to 6 weeks, or until 1 year after stent placement depending on the type of stent (36). Clopidogrel, has superseded ticlopidin, because it is as efficacious but less toxic. Given at the daily dose of 75 mg, it takes about 3 days to attain a complete antiplatelet effect. The onset of pharmacologic action can be accelerated by giving a large loading dose. The considerable interpatient variability in response remains an important issue. A new thienopyridyl compound, prasugrel, which is characterized by a greater potency and faster onset of action compared with clopidogrel, is currently under clinical evaluation. Two direct and reversible P2Y₁₂ antagonists, canagrelor and AZD6140, feature very rapid onset and reversal of platelet inhibition, which make them attractive alternatives to the thienopyridines, especially when rapid inhibition of platelet aggregation or its quick reversal are required. Along with the new P2Y₁₂ antagonists, inhibitors of the other platelet receptor for ADP, the P2Y₁ antagonists, are under development and may prove to be effective antithrombotic agents (9). The parenterally available GPIIb/IIIa antagonists are indicated in the prevention of death and myocardial infarction (eptifibatide/tirofiban) and the prevention of coronary angioplasty complications (abciximab).

The biological control of antiplatelet drugs

Haemogram monitoring is not necessary for clopidogrel in contrast to ticlopidin. In contrast, monitoring of platelet count is required after the administration of GPIIb/IIIa inhibitors as thrombocytopenia might be encountered soon after initiating therapy, although this is more likely to occur with abciximab. No routine monitoring system is available to quantify the magnitude of platelet

dysfunction, but two point-of-care tests may be of interest to monitor the efficacy of the antiplatelet effect, to detect resistance to treatment, and also to predict the bleeding risk during invasive procedures.

1. Platelet Function Analyser - PFA 100®

PFA-100® (Dade Behring, Miami, FL) is a microprocessor-controlled device that provides an *in vitro* quantitative measure of platelet-related haemostasis. The PFA-100 creates an artificial vessel consisting of a bioactive membrane, reproducing the *in vivo* bleeding test. A controlled negative pressure aspirates anticoagulated blood with sodium citrate across a microscopic aperture cut into the membrane under steady high shear rates. The membrane is coated with collagen and either epinephrine bitartrate, 10 mcg, or adenosine-5'-diphosphate, 50 mcg (ADP). The presence of a platelet antagonist and the high shear stress results in a platelet plug that gradually occludes the aperture. The time required to obtain full occlusion of the aperture is defined as the collagen/ADP closure time (CACT) or collagen/epinephrine closure time (CECT). Measurements of closure time by the PFA-100 depend on functional platelets, GPIb and GPIIb/IIIa, von Willebrand factor, platelet count, and haematocrit (25). PFA-100® performed with an epinephrine-collagen (EPI-C) cartridge is sensitive to aspirin administration though the test cannot be used to predict the haemorrhagic risk associated with aspirin (14, 15, 42). The PFA-100® is not able to detect patients treated with clopidogrel, probably because a platelet plug is still generated by the high amounts of ADP (50 mcg) contained in the ADP cartridge (1).

2. The thromboelastogram (TEG)

The thromboelastogram, TEG® (Haemoscope Corp., Niles, IL), which can be used as a near-patient device, analyses the visco-elastic properties of whole blood. It is currently used in cardiac and liver surgery, obstetrics, and intensive care as well as in trauma centres. In contrast to clotting tests, which by definition detect only a clotting time, TEG detects all phases of the coagulation process and fibrinolysis by measuring the change of elasticity during clotting and fibrinolysis. TEG detects the clot firmness, i.e., the clot's mechanical stability. As the test is performed on whole blood, it detects the interaction of plasma factors, platelets and other cells, such as the participation of red

cells in haemostasis. Accordingly, the thromboelastograph has proven itself as a useful tool in studies of clot lysis, of red blood cell and platelet interactions, detection of the hypercoagulation state, and the determination of clot structure and stiffness (29). The r time is the time taken for the first fibrin strands to form, the Maximal Amplitude (MA) is the maximum strength of the clot. The alpha angle and k time reflect the kinetics of clot development. Finally, retraction of the clot occurs with eventual lysis, the Ly30 being a function of this (29).

The TEG demonstrates certain platelet aggregation defects, including post-cardiopulmonary bypass-induced platelet dysfunction related to glycoprotein GPIIb/IIIa receptors (24). Because of the overwhelming presence of thrombin generation, conventional TEG is not able to detect the platelet defect that occurs with aspirin or clopidogrel and demonstrates a normal MA on TEG. The newly modified TEG assay (mTEG®, Haemoscope Corp., Niles, IL) generates clot without thrombin generation using reptilase and FXIIIa (activator F), thereby overcoming this limitation. The addition of a platelet agonist enables measurement of the degree of platelet inhibition resulting from aspirin or clopidogrel or both. Testing is performed on heparinised blood. Two traces are run concurrently. One is of heparinised blood treated with 10 mcl of activator F that measures the contribution of fibrin to the MA and the second is of heparinised whole blood with 10 mcl activator F and 10 mcl agonist (acid arachidonic in the case of aspirin and ADP in the case of clopidogrel). The results are compared with the kaolin heparinase trace. The resulting clot MA is dependent on platelet stimulated by the added agonist. The degree of response to the drug inhibition is dependent on the platelet still being able to be activated and to generate a curve. The closer the curve with agonist is to the curve with kaolin-heparinase, the lower the platelet inhibition. In contrast, the closer the curve with agonist is to the trace of the clot generated by fibrin alone, the greater the inhibition of platelet aggregation. The former situation represents a patient resistant to treatment, the latter is in accordance with an adequate antiplatelet effect (11).

It has been shown very recently that mTEG® can be used to monitor the effect of clopidogrel as well as of aspirin (1). mTEG® shows good agreement with light transmission aggregometry. It potentially has a wide scope for monitoring the effectiveness of therapy as well as being a possible predictor of perioperative bleeding.

Perioperative strategies

The risk of haemorrhage in general surgery is considered to be high in patients treated preoperatively with thienopyridines; however there are scarce data in the literature. In contrast, it has been well demonstrated that the administration of clopidogrel increases the bleeding risk during cardiac surgery (43, 18, 16, 31, 13, 21, 22, 27). Only one study did not report an increased risk of bleeding with preoperative administration of clopidogrel (23). However, in that study the drug was administered early (24 to 48 pre-surgery) without a loading dose. Considering the delayed antiplatelet effect obtained after a standard dose, it was not surprising that no difference in blood loss was observed. Given the increased risk of bleeding, the drug is often stopped at least 7 days before surgery. However, recent publications warn against the withdrawal of antiplatelet agents before surgery as complete recovery of platelet function may place the patient at an increased risk of ischaemic events, particularly important when the patient is having a coronary stent (2, 3, 4, 40). Patients who have undergone coronary stenting less than 35 days earlier should not undergo non-cardiac invasive procedures except in an emergency (10, 40). In the case of dual therapy (aspirin and clopidogrel), aspirin should be continued until the day before surgery and clopidogrel should be withdrawn just 5 days before surgery. Treatment should be resumed as soon as possible in the postoperative period preferably with a loading dose of clopidogrel of at least 300 mg. If the bleeding risk is estimated to be high, a longer period of withdrawal is foreseen and drug substitution considered. Although both heparins and non-steroidal anti-inflammatory drugs (NSAIDs) have been proposed for this purpose, there are no data to favour one over the other. Moreover, Vincenzi et al. have even shown that heparin does not protect against ischaemic events in patients with coronary stents (40). The French Task Force group has proposed NSAIDs, such as flurbiprofen, but as with the general recommendations, there is no high level evidence to support this proposal (4). In cardiac surgery, aprotinin has been shown to protect against the bleeding risk in a randomised controlled study (38). However, due to controversies concerning its use (30), administration of aprotinin has to be clearly documented and the patient carefully followed (FDA advisory, www.FDA.org). If bleeding occurs, platelet transfusions (0.1×10^{11} /kg body weight, 1 unit of platelets from plateletpheresis) is effective to reduce or stop

peri-operative blood loss in patients treated with antiplatelet agents, although again there is no level I or II evidence to support this. In patients requiring a neurosurgical intervention, laminectomy or invasive procedure on the prostate, prophylactic platelet transfusion could even be discussed.

Platelet transfusion has been demonstrated to be effective in patients treated with abciximab; however, it seems not to be as effective in patients treated with the irreversible GPIIb/IIIa antagonists, tirofiban or eptifibatid³⁴. However, their use should not be a concern in invasive procedures as their half-life is so short. Moreover, Bizzari et al. showed that tirofiban did not increase blood loss in cardiac surgery, and suggested this was not only because of its short half-life but also a possible protective effect of the platelet membrane exposed to cardiopulmonary bypass (CPB) (7). However, these drugs are generally given in combination with aspirin, clopidogrel and heparin, and the effects of these other drugs must, therefore, be considered.

ANTICOAGULANTS

Current anticoagulant therapy is dominated by parenteral heparin and oral warfarin, which act by indirectly inhibiting several steps of the coagulation pathway. The characteristics of an ideal anticoagulant should be a high efficacy-to-safety index, a predictable dose response that allows fixed dosing without the need for laboratory monitoring, administration by oral and parenteral routes, a rapid onset of action, the availability of a safe antidote, and minimal interaction with other drugs and diet. New anticoagulant strategies to inhibit thrombogenesis focus on blocking initiation of coagulation, and preventing thrombin generation and thrombin propagation (Table 1). Initiation of coagulation can be inhibited by agents that target the factor VIIa/ tissue factor complex (FVIIa/TF), whereas thrombin generation can be blocked by drugs that target the specific factors IIa and Xa or by inactivation of factors Va and VIIIa. Direct thrombin inhibitors not only prevent fibrin formation but also block thrombin-mediated feedback activation of FV, FVIII and FXI and attenuate platelet aggregation. Two areas are under particular investigation: specific inhibition, direct or indirect, of factor Xa and factor IIa.

Inhibitors of factor Xa

Selective FXa inhibitors can be classified as indirect and direct inhibitors. Indirect agents

Table 1

<i>Mode of action</i>	<i>Drugs</i>	<i>Development project</i>
	Initiation	
TF/FVIIa complex	Tifacogin (TFPI)	Sepsis (phase III) Not developed further for this indication tested actually in acquired pneumonia
Binds to FX and FXa and inhibits FVIIa within the TF/VIIa complex	NAPc2	Prevention of VTE after elective knee surgery (phase II) Unstable angina or non-STEMI (in combination with aspirin, clopidogrel and heparins with or without GPIIb/IIIa) (phase II)
Competitive inhibitor of FVIIa for TF binding FVIIai is an inactivated form of FVIIa	FVIIai	In patients undergoing PCI (phase II : with or without heparin) Not developed further for the treatment of arterial thrombosis
	Propagation	
Inhibitor of FIXa	TPP-889	Never reached phase II evaluation
Indirect inhibitor of FXa Enhances the inactivation of FXa by AT	Fondaparinux (Arixtra®, Sanofi)	Licensed for VTE thrombophylaxis in high-risk orthopedic surgery and for initial treatment of VTE as an alternative to heparins
	Idraparinux	2,5 mg (phase III) dose-dependant effect
	SSR 126517E	
Direct anti-FXa I both free and bound FXa	DX-9065a (parenteral IV) (reversibly binding)	CAD , PCI (phase I and II) – not developed further
	Razaxaban (oral) Competitive inhibitor	Knee arthroplasty (Phase II) ,- development halted - dose response with respect of major bleeding compared to enoxaparin
	Apixaban	Phase II completed
	<i>Rivaroxaban (BAY-59-7939) oral</i>	Phase II dose-finding study for thrombophylaxis in patients undergoing elective hip and knee arthroplasty and for treatment of DVT – similar thrombophylaxis to enoxaparin but dose trend with respect of major bleeding compared to enoxaparin. No dose response on the prevention of venous TE but dose response with respect to bleeding (dose chosen to investigate 10 mg)
	LY-51 7717	Phase II thrombophylaxis in patients undergoing elective hip and knee arthroplasty and for treatment of DVT- dose finding necessary
	BMS-562247	Phase II
	DU 176b (oral)	Phase II
FVa and FVIIIa inhibitors through the PC-PS pathway	Protein C,	
	APC (recombinant activated protein C, drotrecogin alpha, Xigris®),	Licensed for adults in severe sepsis
Increase the activation of PC in APC by binding thrombin	Soluble Thrombomodulin	Phase II dose-finding study for thrombophylaxis in patients undergoing elective hip and knee arthroplasty
	Thrombin inhibitors	
Direct thrombin inhibitor binds to free and fibrin-bound thrombin	Lepiridun (Refludan®)	Licensed for patients with HIT type II
	Desirudin (Revasc®)	
	Argatroban	
	Bivalirudin	
	Ximelagatran Prodrug of Melagatran (Exanta®) competitive inhibitor	Development halted since February 2006 by Astra Zeneca
	Dabigatran etexilate (BIBR 1048) Prodrug of Dabigatran	phase II trial for the prevention of VTE following hip and knee replacement (BISTRO II). Phase III trials ongoing for thrombophylaxis of VTE in major orthopedic surger, in treatment of VTE, and treatment of stroke

Tissue Factor pathway inhibitor with fondaparinux as a stand.
STEMI : ST-elevation myocardial infarction.
AT : antithrombin.

Table 2

Feature	LMWH	Fondaparinux	Idraparinux
Production	Natural	Synthetic	Synthetic
Bioavailability	80-90%	100%	100%
Half-life (h)	4	17 *	80
Administration	Once or twice a day	Once a day	Once a week
Route of administration	Sc	Sc	sc
Target	FXa and FIIa	FXa	FXa
Renal clearance	Yes	Yes	yes
Neutralised by PF4	Little	No	no
Potential for HIT	Low	No	no
Possibility of neutralisation	protamine sulfate only partial	None rFVIIa ? heparinase ?	none rFVIIa ?

* dose-independent providing normal creatinin clearance.

require antithrombin to inhibit FXa. Novel anticoagulants include parenteral analogs of the pentasaccharide sequence of heparin and LMWH, which mediates its interaction with antithrombin. Fondaparinux, the first synthetic pentasaccharide, binds antithrombin (AT) with high activity. Fondaparinux has a higher specific antifactor Xa than heparin or LMWH and a longer half-life (Table 2). Although fondaparinux may induce the formation of antiplatelet factor 4 (PF4)/heparin antibodies, fondaparinux is unlikely to cause heparin-induced thrombocytopenia type II (HIT II), because it is poorly recognized by the generated antibodies. Moreover, it does not cross react with sera of patients with HIT. Few data indicate that Fondaparinux for patients with documented HITII. Fondaparinux cannot be recommended in pregnancy because scared data. Fondaparinux produces a predictable anticoagulant response and exhibits linear pharmacokinetics when given in subcutaneous doses of 2 to 8 mg. Fondaparinux is licensed for prevention of venous thromboembolism (VTE) after major orthopaedic surgery and for initial treatment of patients with VTE. In high-risk orthopaedic patients, but not in general surgery patients, fondaparinux is superior to LMWH in the prevention of thromboembolic disease (41). The prophylactic dose is of 2,5 mg sub-cutaneous (sc) administered once a day and no dose adjustment is necessary for patients weighting between 50 and 90 kg. However, particular attention should be paid for patients outside these limits, advanced age, and patients presenting an impaired renal function. For the treatment of DVT and PE, a body-weight adjusted, sc dose of 5-10 mg fondaparinux is required. Although fondaparinux has been approved in Belgium in very

high risk patients it is no longer covered by the medical insurance due to its high cost.

Idraparinux is a derivative of fondaparinux that binds antithrombin with such high affinity that it has a plasma half-life of 80 hours (Table 2). Idraparinux produces a predictable anticoagulation response and can be given without coagulation monitoring. However, its long-action may be a concern to anaesthesiologists and surgeons. Idraparinux is administered subcutaneously once-weekly and there is a clear dose-response with respect to major bleeding. A trial comparing idraparinux to warfarin for the prevention of cardioembolic events in patients with atrial fibrillation was stopped prematurely because of excess bleeding in those randomised to idraparinux. A study comparing idraparinux with heparin followed by warfarin for treatment of VTE and PE has recently been completed and the results are awaited.

Direct Inhibitors of factor IIa

Direct thrombin inhibitors (DTI) differ from other anticoagulants in that they bind free thrombin and clot-bound thrombin directly, do not target other factors in the coagulation cascade, and do not require antithrombin as a cofactor (5, 6, 41). Properties of DTI are summarised table 3. Parenteral thrombin inhibitors currently available include lepirudin, argatroban, and bivalirudin. These inhibitors have a great advantage over heparin in that they can be administered to patients with HIT type II. However, because of the parenteral route of administration, frequent monitoring requirements, and absence of an available antidote, these agents are only used in this particular setting.

Table 3
Direct Thrombin Inhibitors

DTI	FIIa binding	Drug	route	Elimination half-life	Pharmacological properties	Monitoring	Antagonist	Efficacy proved
U N I V A L E N T	R E V E R S I B L E	Dabigatran etexilate	Oral	12 h	Independent from factors such as age, body weight, hepatic function and mild-to moderate renal function No drug interactions	No need due to pharmacological properties		Not yet
		Melagatran	Sc, IV	3-5 h				
	I R R E V E R S I B L E	Xi-melagatran*	Oral	35-45 min	Independent of renal function Mainly hepatic	ECT, aPTT : 1.5 -3x the baseline levels is considered therapeutic	NA, although rFVIIa, desmopressin, vWF and PCC have been studied with mixed results	- HIT associated thrombosis - Anticoagulation during PCI
		Argatroban						
B I V A L E N T	I R R E V E R S I B L E	Lepirudin	IV	1.3- 2 h	Dependent of renal function Anaphylactic reaction after read-ministration within 3 months	APTT ACT ECT		- Treatment of HIT - Anticoagulation during CPB - Thrombolytic after orthopaedic surgery
		Desirudin		25-30 min	Less influenced by renal function as extrarenal metabolism exist Cross-reactivity with anti-hirudin antibodies possible but less immunogenic potential			
		Bivalirudin						

DTI : direct thrombin inhibitors, FIIa : thrombin , Sc : sub cutaneous, IV : intravenous, PF4 : platelet factor 4, ECT : ecarin clotting time, aPTT : activated partial thromboplastin time, ACT : activated clotting time, NA : not available, rFVIIa : recombinant activated factor VII, vWF : von Willebrand Factor concentrates, PCC : prothrombin complex concentrates, PCI : percutaneous coronary interventions, CPB : cardiopulmonary bypass.

*Melagatran and xi-Melagatran is no more developed since February 2006 (Astra Zeneca decision).

All DTI are indicated in HIT type II patients as none of these agents interact with PF4.

Ximelagatran, the prodrug of melagatran, a potent competitive thrombin inhibitor, was the first oral direct thrombin inhibitor available and has been shown to be as effective and safe as warfarin for prevention of cardioembolic events in patients with atrial fibrillation. Designed to provide more streamlined anticoagulation than warfarin, this agent can be given without routine coagulation monitoring. The advantages, highly attractive, of ximelagatran over warfarin encompass little inter-individual variability, a rapid onset of action, few diet and drug interactions, and a predictable anticoagulant response without the need for laboratory monitoring. Ximelagatran is not associated with immune-mediated thrombocytopenia. However, in February 2006, Astra Zeneca withdrew the drug from development (<http://www.astrazeneca.com/pressrelease/5217.aspx>), principally because of the worrying elevation in liver function tests in patients receiving long-term therapy (up to 7.9% of patients) and a potential rebound hypercoagulability after treatment cessation. Whether other direct thrombin inhibitors or inhibitors of factors Xa or IXa also have this problem is under investigation.

Monitoring

Because of the high predictability of FXa inhibitors, they can be given without monitoring when administered at prophylactic dose. The anticoagulant effect of fondaparinux is reliably monitored by the anti-FXa activity, which is recommended to have returned to normal before surgery or application of neuroaxial anaesthetic (12). Like LMWH, fondaparinux has no or little effect on the activated partial thromboplastin time (aPTT) or prothrombin time (PT). Administered in a single subcutaneous daily dose, it carries no risk of thrombocytopenia.

Monitoring is more complicated for the oral thrombin inhibitors. These agents have variable effects on routine tests of coagulation and none of the routine tests provides a good estimate of drug level. Although the ecarin (a direct thrombin activator) clotting time (ECT) may be useful to monitor direct thrombin inhibitors, the test is not available in all laboratories and it has yet to be standardised (8). Dabigatran etexilate prolongs the aPTT, but its effects are not dose-dependent. It has minimal effect on the INR, but prolongs the ECT in a concentration-dependent fashion (28). In coronary angioplasty intervention, the Thromboelastography used with ecarin to initiate coagulation and measured, as the reaction time was shown to be more

useful than the standard activated clotting time (ACT) for monitoring bivalirudin anticoagulation across the clinically therapeutic range (8). Although the new anticoagulants have been designed to be given without coagulation monitoring, there are instances where monitoring may be helpful. Reliable monitoring device may help to quantify the anticoagulation effect if renal impairment occurs or to identify reason for bleeding, for patients with treatment failure, and to investigate a patient's compliance with treatment.

Perioperative strategies

Only fondaparinux will be discussed, as it is the only drug currently available in clinical practice. Dose finding studies have shown a dose-dependent increase in the bleeding risk in patients undergoing orthopaedic surgery (37). Administration of a sc standard dose of 2.5 mg fondaparinux more than 6 hours after surgery did not increase blood loss compared to enoxaparin. For neuroaxial blockade, administration of fondaparinux is not a concern as the administration schedule is started only in the postoperative period; no complications were encountered in the study by Turpie et al evaluating more than 7000 patients (37). The patients received single shot spinal anaesthesia precluding any risk of spinal haematoma. However, when there is a bloody tap, it is prudent to delay the administration of fondaparinux or to choose another thromboprophylaxis regimen. In another study, insertion of an indwelling epidural catheter in patients undergoing high-risk abdominal surgery did not lead to neurological complications (17, 39). Timing of catheter removal occurred at least 22 h after the last dose and at least 2 h before the next dose. Data from the EXPERT study (evaluation of arixtra for the prevention of venous thromboembolism in daily practice), suggest that fondaparinux can be omitted the day before the planned catheter removal (epidural or deep peripheral nerve blockade) allowing a time interval of 36-42 h, without an increased risk of thrombosis (17). Should bleeding occur, rFVIIa (Novoseven®, Novonordisk, Denmark) in combination with tranexamic acid has been shown to be effective in a single case report (19).

CONCLUSIONS AND FUTURE DIRECTIONS

Dual therapy with aspirin and clopidogrel will be increasingly encountered in patients undergoing surgery. Withdrawal of both therapies, or at least of

clopidogrel, 5 to 7 days before surgery has been the standard management until recently. Life threatening cardiac complications occurring in the postoperative period in patients undergoing coronary stent placement, often prompted the cancellation of non-cardiac, non urgent surgery for 6 weeks to one year after stent placement depending on the type of stent. Particular attention has been paid to the problem of stopping antiplatelet agents in order to protect the patient from increased bleeding, although more harm may have been done by placing the patient at an increased risk of coronary thrombosis. The balance between the haemorrhagic and the thrombotic risk must always be carefully evaluated by the surgeon, cardiologist, and anaesthesiologist.

Research into new anticoagulants continues ; an ideal agent would be one with increased efficacy and a decreased risk of bleeding.

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